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10/565,763	06/05/2006	Vincenzo De Leo	SER-105	2323

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SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614

EXAMINER	
BORGEEST, CHRISTINA M	
ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/565,763	DE LEO ET AL.	
	Examiner	Art Unit	
	Christina Borgeest	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12 and 14-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12 and 14-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

The amendment filed 22 December 2008 is acknowledged. Claim 12 is amended. Claim 13 is cancelled. Claims 12 and 14-29 are under examination.

Rejections Withdrawn

Claim Rejections - 35 USC § 112, second paragraph

The rejection of claims 12-29 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention as set forth at p. 2 of the Office action mailed 3 October 2008 is withdrawn in response to Applicants' amendment of independent claim 12 to include the active step of the claimed method and in response to Applicants' cancellation of claim 13.

Claim Rejections - 35 USC § 112, first paragraph

The rejection of claims 12-29 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is withdrawn in response to Applicants' arguments regarding their working examples (specifically, p. 5, last paragraph, that the treated population was also utilized as the control population in that the variation of the percentage of total aneupolidy, diploidy and total disomy for each of the treated

populations was measured at the different stages of the treatment regime, i.e. 45 days before the treatment; the day of treatment; and 90 days after the beginning of the treatment. The rejection of claim 13 is withdrawn in response to Applicants' cancellation of claim 13.

Claim Rejections - 35 USC § 102

The rejection of claims 13 under 35 U.S.C. 102(b) as being anticipated by Foresta et al. (Fertil Steril. 2002, 77: 238-244—of record) is withdrawn in response to Applicants' cancellation of claim 13.

The rejection of claims 13 under 35 U.S.C. 102(b) as being anticipated by Acosta et al. (Fertil Steril. 1991; 55: 1150-6) is withdrawn in response to Applicants' cancellation of claim 13.

Maintained Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claims 12, 14-27 and 29 under 35 U.S.C. 102(b) as being anticipated by Foresta et al. (Fertil Steril. 2002, 77: 238-244—of record) is maintained

for reasons of record and the following. Applicants amended independent claim 12 to include the active method step "wherein the effective amount is sufficient to reduce or treat the rate of gamete numerical chromosomal alteration in the male," and the claims can no longer be reasonably interpreted as administration of FSH to males for any reason. Nevertheless, the limitations of the amended claims are still inherent in the teachings of Foresta et al. as evidenced by McInnes et al. (Hum Reprod. 1998; 13: 2787-90). McInnes et al. provides evidence that oligozoospermic males have a higher incidence of "gamete numerical chromosomal alterations," discussed in greater detail below.

As stated at p. 8, 2nd paragraph of the Office action mailed 3 October 2008, Foresta et al. teach the successful treatment of oligozoospermic males with normal basal FSH levels with recombinant FSH or rFSH (see p. 244, left column, last paragraph) at a dose of 100 IU on alternate days (see p. 243, right column, 2nd paragraph), thus meeting the claim limitations of claims 12-27 and 29, because in the context of this rejection, the phrase "at or about 150 IU/dose" is given its broadest reasonable interpretation, and 100 IU is "at or about 150 IU/dose." Foresta et al. is silent with respect to the patients having "gamete numerical chromosomal alterations," however, McInnes et al. provide evidence that "there is increased frequency of sex chromosomal aneuploidy in spermatozoa of infertile men (particularly with oligozoospermia or OAT patients—see for example, p. 2789, right column, last paragraph). In addition, McInnes et al. provide evidence that there is increased diploidy in the OAT patients (see p. 2789, left column, last paragraph). In other words

oligozoospermic males have a higher rate of sex chromosomal aneuploidy and diploidy in spermatozoa, which is to say a higher rate of "gamete numerical chromosomal alterations." Since Foresta et al. teach the treatment of oligozoospermic males with rFSH, and McInnes et al. provide evidence that oligozoospermic males have an increased frequency of chromosomal aneuploidy and diploidy in their spermatozoa, it is evident that the amended claims are inherent in the teachings of Foresta et al. because Foresta et al. are administering the same compound to the same patient population, and furthermore, are doing so successfully, hence they meet the new limitation of claim 12, namely that the effective amount of FSH is sufficient to treat the rate of gamete numerical chromosomal alteration in the male. Arguments are further addressed below.

The rejection of claims 12, 14-17, 19-27 and 29 under 35 U.S.C. 102(b) as being anticipated by Acosta et al. (Fertil Steril. 1991; 55: 1150-6—of record) is maintained for reasons of record and the following. Applicants amended independent claim 12 to include the active method step "wherein the effective amount is sufficient to reduce or treat the rate of gamete numerical chromosomal alteration in the male," and the claims can no longer be reasonably interpreted as administration of FSH to males for any reason. Nevertheless, the limitations of the amended claims are still inherent in the teachings of Acosta et al., as evidenced by McInnes et al. (Hum Reprod. 1998; 13: 2787-90). McInnes et al. provides evidence that oligozoospermic males have a higher incidence of "gamete numerical chromosomal alterations," discussed in greater detail below.

As stated in the Office action mailed 3 October 2008, Acosta et al. teach treatment of infertile males with pure FSH at a dose of 150 IU three times a week for 3 months with the result that six healthy, full-term pregnancies were achieved (see abstract; p. 1151, right column, last full paragraph; p. 1154, right column, penultimate paragraph; p. 1155, right column, 4th paragraph). In addition, Acosta et al. teach that basal sperm concentration values in men with normal FSH levels was higher than those with elevated FSH levels, and that men with elevated FSH levels had only a sperm concentration at an average of 6×10^6, which is evidence of oligozoospermia, or low sperm count (see p. 1154, left column, 2nd paragraph). Furthermore, Acosta et al. meet the exact limitations of the dose of FSH (between 75-300 IU/dose or 150 IU/dose) and frequency of administration (i.e., three times a week or every other day). Note that in this rejection, "at or about 150 IU/dose" is interpreted more narrowly.

Acosta et al. are silent with respect to the patients having "gamete numerical chromosomal alterations." McInnes et al. provide evidence that "there is increased frequency of sex chromosomal aneuploidy in spermatozoa of infertile men (particularly with oligozoospermia or OAT patients—see for example, p. 2789, right column, last paragraph). In addition, McInnes et al. provide evidence that there is increased diploidy in the OAT patients (see p. 2789, left column, last paragraph). In other words oligozoospermic males have a higher rate of sex chromosomal aneuploidy and diploidy in spermatozoa, which is to say a higher rate of "gamete numerical chromosomal alterations." Since Acosta et al. teach the treatment of oligozoospermic males with FSH, and McInnes et al. provide evidence that oligozoospermic males have an

increased frequency of chromosomal aneuploidy and diploidy in their spermatozoa, it is evident that Accosta et al. are administering the same compound to the same patient population, and furthermore, are doing so successfully, hence they meet the new limitation of claim 12, namely that the effective amount of FSH is sufficient to treat the rate of gamete numerical chromosomal alteration in the male. Arguments are further addressed below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The rejection of claim 28 is under 35 U.S.C. 103(a) as being unpatentable over Acosta et al. (cited above—of record) and as applied to claims 12-17, 19-27 and 29

above and further in view of Bouloux et al. (Human Reprod. 2001, 16: 1592-1597) is maintained for reasons of record and the following.

The first issue that must be examined when considering obviousness is to determine the scope and contents of the prior art. The discussion in the preceding rejection of how Acosta et al. meet the limitations of the claims and how the new limitations are inherent by Acosta et al. as evidenced by McInnes et al. is applicable here and is hereby incorporated. The second issue is to ascertain the differences between the prior art and the claims at issue. Acosta et al. do not teach the administration of CTP-FSH, which is a variant of FSH. Bouloux et al. teach that CTP-FSH is safe and effective because it could lead to more convenient dosing regimens (i.e., the longer half life decreases the need for frequent injections—see p. 1592, right column, and p. 1596, right column, last paragraph). Given this teaching, it would be obvious to one of ordinary skill in the prior art (the POSITA) to substitute CTP-FSH for FSH because the level of skill in the art concerning knowledge of FSH variants and determining dosing regimens for variants is high, and given the evidence presented in Bouloux et al. that the FSH-CTP was well tolerated, the POSITA could expect to substitute one FSH variant for another with a reasonable expectation of success. Arguments are further addressed below.

Response to Arguments

At p. 6, last full paragraph Applicants argue that both Foresta et al. and Acosta et al. are silent with respect to patients having chromosomal abnormalities such as sperm diploidy, disomy and aneuploidy, thus do not anticipate the claimed invention.

This argument has been considered and in response to Applicants' amendment of their independent claim to recite the active method step and thus require the reduction or treatment of the male having gamete numerical chromosomal alterations, the Examiner has provided evidence that both Foresta et al. and Acosta et al. (In the form of McInnes et al.) were treating the same patient population with the same agent. McInnes et al. is extrinsic evidence that shows that the new limitation in the claims requiring treatment of "gamete numerical chromosomal alterations" was inherent to both the teachings of Foresta et al. and Acosta et al. because McInnes et al. makes clear that the missing descriptive matter, namely, a discussion of "gamete numerical chromosomal alterations" was necessarily present in both Foresta et al. and Acosta et al. As stated above, McInnes et al. provide evidence that "there is increased frequency of chromosomal aneuploidy in spermatozoa of infertile men (particularly with oligozoospermia or OAT patients—see for example, p. 2789, right column, last paragraph) ***and*** that there is increased diploidy in the OAT patients (see p. 2789, left column, last paragraph). In other words oligozoospermic males have a higher rate of chromosomal aneuploidy and diploidy in spermatozoa, which is to say a higher rate of "gamete numerical chromosomal alterations."

At p. 7, 3rd paragraph, Applicants argue that the Bouloux et al. reference does not cure the defect of the Acosta et al. reference (i.e. Acosta et al. are silent with respect to patients having chromosomal abnormalities such as sperm diploidy, disomy and aneuploidy).

This argument has been considered and in response to Applicants' amendment of their independent claim to recite the active method step and thus require the reduction or treatment of the male having gamete numerical chromosomal alterations,

the Examiner has provided evidence that both Foresta et al. and Acosta et al. (In the form of McInnes et al.) were treating the same patient population with the same agent. McInnes et al. is extrinsic evidence that shows that the new limitation in the claims requiring treatment of "gamete numerical chromosomal alterations" was inherent to both the teachings of Foresta et al. and Acosta et al. because McInnes et al. makes clear that the missing descriptive matter, namely, a discussion of "gamete numerical chromosomal alterations" was necessarily present in both Foresta et al. and Acosta et al. As stated above, McInnes et al. provide evidence that "there is increased frequency of chromosomal aneuploidy in spermatozoa of infertile men (particularly with oligozoospermia or OAT patients—see for example, p. 2789, right column, last paragraph) ***and*** that there is increased diploidy in the OAT patients (see p. 2789, left column, last paragraph). In other words oligozoospermic males have a higher rate of chromosomal aneuploidy and diploidy in spermatozoa, which is to say a higher rate of "gamete numerical chromosomal alterations." Furthermore, the teachings of McInnes et al. make it clear that it would be so recognized by persons of ordinary skill in the art that oligozoospermic men have higher rates of sperm aneuploidy and diploidy.

At p. 7, 3rd paragraph, Applicants argue that "at page 4, the Office Action [mailed 3 October 2008] indicates that the art teaches that elevated FSH levels in males is correlated with high levels of sperm chromosomal abnormalities, and thus 'does not suggest to one of skill in the art that treatment of these disorders can be achieved by administering more of the very substance to patients that they have too much of.'"

This argument has been fully considered, but is no longer relevant since the rejection under 35 U.S.C. 112, first paragraph was withdrawn.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is (571)272-4482. The examiner can normally be reached on 9:00am - 3:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Christina Borgeest

/Jeffrey Stucker/

Supervisory Patent Examiner, Art Unit 1649